Anti-Infective Drug Advisory Committee

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

"Safety and Efficacy of 1-Day and 3-Day Dosing Regimens of Azithromycin Suspension (New Drug Application 50-710, Pfizer Inc.) for the Treatment of Otitis Media"

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P R O C E E D I N G S 8:00 AM

DR. RELLER: Good morning. Welcome to the Anti-Infective Advisory Committee meeting, the principal topic, safety and efficacy of 1-day, 3-day dosing regimens of azithromycin suspension for the treatment of otitis media.

We will begin today's meeting with an opening statement from our Executive Secretary, Tom Perez. MR. PEREZ: Good morning. The following announcement addresses conflict of interest with regard to this meeting and is made part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interests reported by the Committee participants it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest at this meeting with the following exceptions.

In accordance 18 USC 208(b)(3) full waivers have been granted to Dr. Steve Ebert and Dr. James Leggett to participate in the discussions of the new drug application 50-710 for the treatment of otitis media.

In accordance with 18 USC 208(b)(3) general matters waivers have been granted to all participants with

the exceptions of Dr. Steve Ebert, Dr. Ellen Wald and Dr. Mary Glode to participate in the general matters discussion of clinical trials of acute otitis media.

Drs. Ebert, Wald and Glode are excluded from this discussion. A copy of these waiver statements may be obtained by submitting a written request to the agency's Freedom of Information Office, Room 12A30, Parklawn Building.

With respect to FDA's invited guests, Dr. Colin Marchant and Dr. Jan Patterson have reported interests which we believe should be made public to allow the participants to objectively evaluate their comments.

Dr. Marchant would like to disclose that he serves as a speaker for Bristol-Myers Squibb; Glaxo, Smith, Kline, Roche and Wyeth Ayerst. He consults for Aventis(?) Biovel(?) Bristol-Myers Squibb, Glaxo, Smith, Kline, the Robert Wood Johnson Pharmaceutical Research Institute and Wyeth Ayerst. He is, also, an investigator on research contracts, grants received from Bristol-Myers Squibb, Glaxo, Smith, Kline and Wyeth Ayerst.

Dr. Patterson would like to disclose that she serves as a speaker for Wyeth Ayerst, Merck and Aventis. She is a consultant to Pfizer, Merck, Fusisawa(?) and Schering Plough. She, also, serves on the Clinical Anti-

Infective Advisory Boards for Pfizer, Wyeth, Ayerst and Estraseneca(?).

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the record.

With respect to all other participants we ask in the interests of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment upon.

Thank you.

DR. RELLER: Thank you, Tom.

Next, I would like to have the members around the table introduce themselves briefly and their position. We will start with Dr. Mark Goldberger at my far right.

DR. GOLDBERGER: Mark Goldberger, the Acting Office Director for Ode-4(?).

DR. SORETH: Janice Soreth, Acting Division Director for Anti-Infectives.

DR. ALEXANDER: John Alexander, medical officer in the Division of Anti-Infectives.

DR.MOLEDINA: Nesim Moledina, medical officer for

anti-infectives.

DR. WALD: Ellen Wald, Chief of Infectious Diseases at the Children's Hospital of Pittsburgh.

DR. LEGGETT: Jim Leggett, Infectious Diseases, Providence Portland Medical Center in Oregon Health and Sciences University.

DR. O'FALLON: Judith O'Fallon, statistician at the Mayo Cancer Center.

DR. CHRISTIE-SAMUELS: Celia Christie, Professor and Chair, Pediatrics, University Hospital of the West Indies, University of the West Indies, consultant in pediatric infectious diseases, epidemiology and public health.

DR. CHESNEY: John Chesney, professor of pediatrics at the University of Tennessee in Memphis and Infectious Disease Division.

DR. RELLER: Barth Reller, Division of Infectious Diseases, Director of Clinical Microbiology, Duke University Medical Center.

MR. PEREZ: Tom Perez, Executive Secretary for this Advisory Committee meeting.

DR. EBERT: Steven Ebert, Infectious diseases pharmacist, Meriter Hospital and clinical professor, University of Wisconsin, Madison.

DR. CROSS: Alan Cross, professor of medicine, University of Maryland, Division of Infectious Diseases.

DR. GORMAN: Richard Gorman, pediatrician in private practice and a member of the Pediatric Advisory Subcommittee.

DR. GLODE: Mary Glode, I am professor of pediatric infectious disease at Children's Hospital, University of Colorado.

DR. BURNS: Jane Burns, pediatric infectious diseases, University of Washington.

DR. MAXWELL: Celia Maxwell, Assistant Vice President for Health Affairs and associate professor of medicine, Howard University.

DR. PATTERSON: Jan Patterson, infectious diseases at University of Texas Health Science Center, San Antonio and hospital epidemiologist for University Health System in South Texas Veterans Health Care System.

DR. MARCHANT: Colin Marchant, pediatric infectious disease, Boston University and Tufts University School of Medicine in Boston.

DR. RELLER: Dr. Janice Soreth, Acting Director of the Division of Anti-Infective Drug Products will give an introduction to today's meeting.

Janice?

DR. SORETH: Thanks, Dr. Reller.

Members of the Committee, invited guests, colleagues in industry and FDA, ladies and gentlemen, we have a full agenda today. So, I will keep my comments brief.

First, I would like to recognize several of our Advisory Committee members who are completing their term with us and rotating off the Committee.

I would ask you please to come forward and accept a certificate of appreciation from us. They are Dr. Celia Christie, Dr. David Soper and Dr. Joan Chesney.

Could you step forward, please?

Perhaps Dr. Soper is not here yet, and Drs. Barbara Murray and Wittner are, also, not here, but rotating off the Committee.

We very much appreciate your active participation on the Committee, and we fully recognize that in giving us your considered and critical thoughts you add to already full calendars and long days.

As you rotate off the Committee I would simply add that we welcome your comments on the experience as we are always open to your suggestions in improving the process.

Second, I would just like to comment briefly on

today's agenda. We will begin with Dr. Colin Marchant whom we have invited to speak on the dual aspects of clinical trial design in acute otitis media, an issue that we periodically revisit. We will then have presentations from the sponsor, Pfizer and from the FDA on azithromycin on the specific data that were developed for single dose or a 3-day treatment regimen for children with acute otitis media conducted in studies that fully correspond to our current guidance document for developing a drug for acute otitis media.

The open public hearing will then follow and three speakers have come forward to present. After lunch we will resume Committee discussions of and voting on the specific data that speak to the efficacy and safety of azithromycin in various treatment regimens for acute otitis media.

Finally, we will round out the day with an FDA presentation that comes back to acute otitis media clinical trial design issues or lessons learned as it were from half a dozen or so meetings that we have had int he past 5 years on acute otitis media either as a general comment on guidance for design or on specific drug products seeking a claim of acute otitis media.

It is not the intent of the last part of today's

meeting to come to any final conclusions. Rather it is intended to serve as a prelude to a future public meeting with an opportunity for all industry, academia and the public to participate where the focus would be on the guidance document itself and whether and how it might be revamped or improved.

Dr. Reller, I turn it back to you.

DR. RELLER: Thank you, Dr. Soreth.

Next we will look forward to hearing Dr. Marchant's presentation.

Dr. Marchant?

DR. MARCHANT: Good morning. Today I will talk about the design of clinical trial and antibiotic therapy for acute otitis media, and my remarks will be of a general nature, and I will not address the particular application before you today.

My remarks are based on our formulation of the issues of clinical trials and I think they are pertinent to the question of comparative trials of acute otitis media.

I won't discuss the obvious issues that we should randomize patients or we should do double-blind trials but rather I am going to focus on the issues of the outcomes we chose in these trials and the implications that result from choosing various outcomes.

Of course, we could use a clinical outcome of symptomatic improvement or a combination of the two, symptomatic and where the clinician examines the eardrum or some combination of these.

The bacteriologic outcome which refers to actually doing a tympanocentesis has shown that there is eradication of the organism from the ear and there can, also, be other combinations of this such as a combined bacteriologic/clinical one where you look at clinical improvement and then do a tympanocentesis to ask in cases where they have found where they have eliminated the organism and then finally is to look at the time of the outcome. It could be during therapy, at the end of therapy or after therapy.

The timing of the outcome is varied, often symptomatic improvement or persistent symptoms have been typically measured at 48 to 72 hours. The trials that did bacteriologic outcome typically were at 4 to 6 days and some trials have looked at symptomatic outcome at that same time. Other trials have looked at end of therapy measuring typically symptomatic outcomes but often measuring events that have occurred throughout this time period and then there is the last outcome which was the test of care where they also consider events that happen after therapy,

recurrences here as your outcome.

To decide how they should study acute otitis media in terms of its clinical response in the face of effective therapy or therapy that you would like to be effective placebo-controlled trials are often very instructive as to what the natural course of disease is and may help you in planning these.

Also, studies which followed clinical outcomes with bacteriologic outcomes are also very instructive in telling us how we should plan these trials.

So, I am going to review some of the data in the literature that speaks to this. This is a randomized placebo-controlled trial done in Denmark looking at children primarily older than age 3 with severe earache. They measured a pain score. They were randomized to placebo or penicillin and you can see here that in the first couple of days there is a significant difference in favor of antibiotic treatment. This was done back in the eighties. So, penicillin shouldn't be so shocking, but you can see there is a difference here, but if you will notice out at day 4 or 5 there is no difference between the treatments. If you are asked whether antibiotics are effective here, you come up with the answer that no, they are not.

If you ask the question here, you will come up

with the answer that yes, they are. So, the timing in relation to how the disease behaves is very important.

Final placebo controls, one of the ways the administration was to have been done is a trial done at the University of Pittsburgh. The trial was done in the early 1980s, comparing amoxicillin, placebo and various combinations of myringotomy. The Pittsburgh trial divided the otitis media in to severe and non-severe based on high fever and marked earache and symptoms.

One of the outcomes they looked at was initial treatment failure at typically 48 hours after starting therapy.

The group did not feel they could do a pure placebo-controlled trial in the severe group. So, they made these three comparisons, and you can see that amoxicillin and amoxicillin and myringotomy turned out pretty similar results, but the placebo and myringotomy there was a larger failure rate and a difference here depending on whether you make this comparison or that comparison of about 12 to 14 percent.

So, in the severe group you see a spread in that sort of range, between 10 and 15 percent.

In the less severe arm of the trial they compared amoxicillin with placebo. Now, instead of a 10 to 15

percent difference in terms of this initial treatment failure you see a difference of only about 4 percent. So, the severity of the disease that you are looking at will determine what your response rate may be.

Also, look here that they were able to show that amoxicillin has a lower rate effusion at 14 days, but that by 6 weeks the difference is washing away. Why? Because recurrences of therapy occur equally in those that received amoxicillin and those that received placebo and what this should suggest to everybody in terms of a scientific experiment; that is what this is, is a randomized scientific experiment is that this outcome here really has nothing to do with whether you have treated or not treated.

Let us explore that further because this is part of the test of cure outcome. Let us look at studies with bacteriologic and clinical correlations. This is a study by Dr. Leibowitz and Dr. Dagan that was presented at ICAC(?) last September. It is the third of three trials that basically show the same idea though because this has a larger number of patients that previous studies it shows it more closely.

What are we looking at here? This is a group of patients treated with antibiotics with tympanocentesis during therapy and that result was sterile but then on

stopping therapy the first week, the second week, third and fourth weeks afterwards there was a clinical recurrence of otitis media that again there was a tympanocentesis to determine what the bacteriology was. This refers to infections as determined by the species, whether it was Pneumococcus or Hemophilus or by pneumococcal serotype or electrophoresis typing of the organisms and for Hemophilus influenzae they either beta-lactamase(?) positive or negative.

What this shows you is that even in the first week the majority of patients had more infections, more relapses of their infection. Those appear at least to be relapses and relapses of the bacteria of pharynx or relapses because the bacteria had persisted in the ear. We have now clinical data to address that situation. The previous data I showed you recurrences occurred at the same rate only in drug and placebo and if you look at a lot of the clinical trials that have looked at this clinical recurrence after therapy, they are the same regardless of the drug that you use. So, here is what you might say about clinical recurrences. They are not reduced by antibiotic therapy. They occur in the patients and new infections are more common than relapses.

So, in clinical trials we are going to be

counting as failures the event that don't appear to have any relation to antibiotic therapy.

Let us now move on to the clinical bacteriologic correlations in double tympanocentesis studies looking at patients where the organism is eradicated for the ear versus those where it persists and look at clinical success defined as symptomatic outcome at the time of the second tympanocentesis.

You see that those that eliminate the bacteria have a much higher cure rate than those where you do not. You will, also, notice that there are some here that still fail therapy despite the fact that you have eliminated the bacteria and other studies suggest that those patients have persistent viral infections that might be responsible for these persistent symptoms.

You will, also, notice now that probability of failure clinically is much higher when bacteria persist. This is data that my colleagues and I did in Cleveland since then using a slightly different approach. Dr.Degan and colleagues did another study, again, looking at bacteriologic eradication, failure here in bacteriologic eradication, then at the clinical status not at days 4 to 6 but between days 4 and 6 and day 10, but they are finding the same thing, and that is you are more likely to fail if

you don't kill those bacteria by day 4 to 6 than if you have eliminated bacteria from the ear.

So, now, I would like to pursue the implications of this. This is the data from Cleveland. The first two lines are the data I just showed you two slides ago in pie diagrams. If you kill bacteria 93 percent success rate. If you don't, 62-1/2, but in clinical studies where you don't do a tympanocentesis you will, also, be looking at non-bacterial otitis media and a response that right there was 80 percent. You can use these data to calculate the clinical behavior of the disease at various levels of bacteriologic efficacy of the drug which led to us describing the Pollyanna phenomenon.

Here is what it shows. Here is efficacy on this axis. Here is elimination of bacteria from the ear and each line adjoins the corresponding clinical response that you see clinically. A perfect drug looks worse than it is. A drug that eliminates bacteria 90 percent of the time looks worse than it really is, and not all drugs of inferior efficacy, down here at the bottom here, the yellow line which is the placebo rate calculated from Dr. Virgil Highley's(?) study all the less active drugs will look better than they are and in this and subsequent slides I am going to represent drugs that appear worse than they are

and drugs appearing better than they are on the right. The predominant effect is to conclude that drugs with poor activity actually work well.

So, now I am off to design issues. Now, we have looked at double tympanocentesis study, single tympanocentesis study measuring clinical efficacy and in the single clinical efficacy you saw on the previous slide. This has very precise implications in terms of the ability of you to do a clinical trial and detect a difference if a difference is there whereas a difference between, well, a difference between say one drug and the other versus a narrow difference it takes fewer patients to show a difference in the clinical trial.

Let us look at that. So, here what I am going to show you is this. If we compare a drug with 90 percent efficacy with drugs that are 30, 40, 50, 60, 70, 80 percent efficacious and lump your different trial designs and use the sample size required to look at that for the bacteriologic outcome less than 100 percent patients are required until you get up to trying to detect a difference between 80 and 90 percent.

If you look at the clinical outcome in bacterial otitis media that is a serotype study now you are able to tell the difference between say 70 percent and 90 percent

is approaching 2000 patients and if you look at clinical outcome with no tympanocentesis extremely large numbers of patients are required.

For those of you, I know there is at least one statistician in the audience, all the sample size calculations that I am doing today I am showing you sort of a significance of .05, a power of .9 as the universal method for calculating sample sizes and all sample sizes are for a two-limb trial with half the subjects in each limb, and so now in subsequent trials I am going to try to draw down and simplify the question.

Various levels of bacteriologic efficacy, 90 percent is about as good as you get with most trials in the literature. We will call this a good drug. Here is the placebo related to approximately that of 30 percent and looking at 50 and 70 percent.

So, I am going to focus our attention on those sorts of differences in bacteriologic efficacy.

So, now I am just going to show you exactly the same graph that I showed you before, but now I am just looking at the three different standards compared to a 90 percent drug and I am going to continue to do that.

The only thing I did was I changed the scale here and topped it out at 2000 patients because nobody has ever

down a trial larger and there is really no point until somebody does of talking about achieving larger sample sizes.

You can see that the clinical outcomes are way off the chart and not feasible. The argument that I am putting forward and have put forward in the literature has been based on the data from Cleveland that my colleagues and I generated. Perhaps that data is very specific to the particular patients that we studied.

So, now, I am going to look at other data in the literature and make similar calculations. So, when I take the Pittsburgh trial I use these standards. They looked at amoxicillin in the early 1980s and we will assume it is about 90 percent efficacious in terms of bacteriologic eradication. That is what the studies would tell you and here is the effusion for outcome, for example. Here is tap water. That is the placebo group and here is their response rate, and all I have done is proportionately calculated these two numbers in between for the fair drug and poor drug standards.

So, now, if we look at the outcomes in the Pittsburgh trial, what do they look like? Here is the bacteriologic standard. Here is the outcome of severe otitis media. They actually looked at myringotomy but that

is using a 14 percent difference, and you can see that with the fair drug you can't tell the difference. With the poor drug you need above 600 patients.

If we look at the middle ear effusion outcome it appears here and if we look at their clinical outcome in non-severe otitis media which was 78 percent of all otitis media you will have a very tough time telling the difference between tap water and a good drug.

So, now we will turn to the test of cure outcome. Here is another one of these Pollyanna graphs,the same bacteriologic outcome here, symptomatic response. Now, when you start to calculate these recurrences against therapy you will see what happens. You progressively make excellent drugs in order that other drugs look worse and worse while your fair drugs still look better than they really are compared to the bacteriologic eradication rate.

I have used a range of numbers here because the recurrence rates are going to vary by the population you look at and your exact time points but that is a pretty wide spread.

What are the sample size implications of that? There is your bacteriologic standard. Here is your clinical outcome and as you add in the clinical occurrences after therapy in test of cure outcome you just make it harder and

harder as you have a higher recurrence rate to show the difference between two drugs.

So, it makes everything look the same. I would now like to turn to some other outcomes. I draw your attention here to the data from Cleveland. We looked at bacteriologic response here and clinical response there whereas Dr.Degan looked at bacteriologic outcome here and clinical response anytime in this interval.

So, during this time after they did the second tympanocentesis the otolaryngologist in this study would evaluate the patients in terms of their symptoms and in terms of the examination of the middle ear, and if they were failing therapy another therapy was described. So, the outcome of failure could occur anywhere from this visit to this visit at the end of therapy. So, that allows us to look at end-of-therapy outcomes particularly the strategy of doing a tap and a tap of failure.

So, here is bacteriologic efficacy, and here we have the bacteriologic outcome in clinical failures the tap and tap of failures. You can see that yes, it has narrowed again but it is a little bit better than just doing a clinical outcome in bacterial cases, and again, this is all using Dr. Degan's data and if we look at the test of cure outcome using approximately a 15 percent rate which is what

he found in his studies, no difference between those where the bacteria were eliminated and those where they weren't and a rate of about 15 percent.

Again, you can see it driving down. So, you can see that the choice of clinical trial design is going to determine where your efficacy is set, but it is, also, going to have an effect on the narrowness of the difference in the size of the trial.

So, here are the outcomes with Dr.Degan's trials.

Bacteriologic, a tap and tap of failures study does a little bit better but it requires still quite large numbers at the 70 versus 90 percent, the fair drug standard and again using the test of pure outcome is going to drive the sample size higher.

So, how important are these? Well, I have talked about a good drug, fair drug, poor drug, tap water. Using the relationship between clinical response and bacteriologic outcome if you treat 1 million children, 1 million prescriptions how many children would have persistent symptoms on day 3 to 6 who otherwise would have been asymptomatic if you had a perfect drug if you eliminated bacteria from the ear? Well, we won't achieve that standard, but here is the good drug standard, 20

percent.

Well, the difference between a good drug and a fair drug is 40,000 children per million prescriptions having persistent symptoms because they got a drug that was less effective than a good drug, and if we go down to tap water the difference is 140,000 minus 20,000 which comes out to 120,000 children who remain symptomatic per million prescriptions who otherwise would be better.

So, now to just draw down the see the numbers as they go by you I am going to look first at the tap water standard and study designs using initial bacteriologic diagnosis. How many patients do you need? You can see that the bacteriologic outcome and the tap and tap of failures do pretty well, clinical outcomes less well. Test of cure obviously drives the sample size from here up to here.

This is the number of patients you analyzed because about 25 percent of otitis media is non-bacterial. This is the number of patients you must recruit. So, this is the work that must be done by the investigators, by the sponsor of the trial, etc.

What about the clinical outcomes now, no tympanocentesis, again the tap water standard? The best we can do comes from the data from the Pittsburgh study with severe cases of otitis media and we are a little under 500.

I now go to data I didn't talk about before and that is Dr.Rich Rosenfeld, an otolaryngologist who is trained in epidemiology who did a meta analysis in his book, evidence-based otitis media or something to that effect, and the best outcome he could come up with in terms of its effect on the disease was clinical resolution in 7 to 14 days and using that calculation again we are all seeing a sort of neighborhood, and if we take non-severe cases we are approaching 2000 patients just to tell a difference between a good drug and tap water.

Moving up to the poor drug standard we see now that tap and tap of failures is still feasible but getting tougher, clinical outcomes going up for bacterial cases. The sample size is almost all in the thousands here for the poor drug standard and if we move to the fair drug standard, well, this is potentially feasible with a bacteriologic outcome but this is now getting extremely difficult and the clinical outcomes are really out of sight.

So, I am going to draw some conclusions because most trials are only 300, 400, 500 patients, 100, 200 patients and so forth, most trials that use bacteriologic diagnosis and clinical outcome have been too small to distinguish between a good drug and tap water and all have

been too small to distinguish between a good drug and a fair drug.

Most trials using clinical diagnosis and a clinical outcome have been too small to distinguish between a good drug and tap water.

Data do not support the use of a test of cure outcome as a scientifically valid outcome in clinical trials of antibacterial drugs for acute otitis media.

Now, the sort or recommendations from this. Clinical trial data in support of licensure of antibiotics for otitis media should at a minimum at least show efficacy, that is distinguish between tap water a good drug.

I think the FDA is already heading in this direction, but again, I encourage that they should convene experts to examine the design of antibiotic trials for otitis media using scientific data and scientific principles as opposed to professional consensus and revise the guidance for industry accordingly.

The problem with the tympanocentesis studies is basically that they are difficult to do at least in the United States. That difficulty relates to the fact that it is a painful procedure and people are reluctant to do two tympanocenteses and if you look at the literature on how we

relieve pain in children for this procedure there are no good studies. There is no good data. There is no standard of care and really in order to do these studies which not only enlighten us in terms of relative drug efficacy but allow us to, also, look at the relationship between the MIC of the organism and eradication and so forth to do these we really need studies looking at systemic or topical analgesia or anesthesia and I suggest that industry might want to become interested in seeing that go on, and because the bacteriologic outcome is not universally accepted and certainly not universally loved mobilize a way to make clinical trials better using clinical outcomes by more sensitive outcomes, enriched populations and these should be investigated in rigorous studies but I caution everybody that large numbers of subjects are likely to still be required if we are going to distinguish between one drug and another.

So, I thank everybody for their attention, and I thank the agency for inviting me to address you today.

Thank you.

DR. RELLER: Thank you, Dr.Marchant for that presentation. That will give new and enlarged insights into the discussion that we have this afternoon on the topic of future approaches to clinical trials for guidance to

industry and investigators that we will cover after the discussions this afternoon.

We now turn to the topic of the rest of this morning's deliberation and the content that will be assessed by the Committee in their vote just after lunch and I at this time would like to introduce the Pfizer presentation about azithromycin and treatment of acute otitis media.

Dr. Michael Dunne, please?

DR. DUNNE: Thank you, Dr.Reller.

Good morning. My name is Michael Dunne, and I am an infectious disease clinician that is responsible for clinical development of anti-infective products at Pfizer.

We appreciate the opportunity this morning to discuss with you the data that support the use of azithromycin given either as a single dose or over 3 days for the treatment of acute otitis media.

I will be presenting an overview of the relevant preclinical data followed by discussion of the clinical trial data that supported the use of azithromycin with the shorter courses.

First, we will begin though with a presentation by Dr.Edward O'Rourke. Dr. O'Rourke is assistant professor of pediatrics at Harvard Medical School and a Director of

Harvard Medical International.

Dr. O'Rourke will give us an overview of acute otitis media specifically focusing on the influence of Streptococcus pneumoniae and Hemophilus on the presenting signs and symptoms, the clinical course of the disease and the secondary complications of acute otitis media.

Dr. O'Rourke?

DR. O'ROURKE: Good morning. Thank you for the opportunity to speak with you today. I am going to talk about otitis which I think all of the pediatricians in the room understand is the most commonly diagnosed bacterial disease in children and the most common reason that antibiotics are prescribed at all.

It, also,is one of the major reasons that we have problems with antibiotic resistance in pediatrics because of the rate at which this diagnosis is made, either correctly or incorrectly and the treatment habits of our pediatricians. When we talk about tracing therapy for otitis media we certainly want to think about what the reasons are that we are treating and which are the pathogens that we should focus on, and in selecting therapy on a rational basis there are several bits of data that we would like to have to understand how to focus. One would be the prevalence of pathogens, both patients who are

untreated and those who are presenting after an antibiotic failure.

We would, also, like to know whether the clinical severity of acute otitis media relates to the pathogen.

Dr. Marchant showed us that some patients have severe disease and may be easier to make an impact on their outcome than those with mild disease.

We would, also, like to know whether untreated infections resolve by themselves and whether that varies by pathogen, where is a risk of complications and whether that varies by pathogen.

We see here a commonly displayed summary of the bacteriological data from Pittsburgh in the 1980s showing that Streptococcus pneumoniae is the most common bacterial pathogen, Hemophilus No. 2, then Moraxella catarrhalis.

In this particular summary of data there were a fairly large number of patients included without bacterial isolates and if we look at data more recently from the same institution we see that in data where there are fewer non-bacterial pathogens in fact Streptococcus pneumoniae is even more prevalent in relation to the other pathogens in otitis media.

If we look at data from the nineties looking at either untreated acute otitis or persistent otitis media,

this data from New York we see again a fair number of patients with no pathogen, Streptococcus pneumoniae clearly more prevalent than Hemophilus influenzae, Moraxella or Group A Streptococcus.

In patients with persistent otitis media again Pneumococcus is the No. 1 bacterial pathogen although there are a large number that do not have pathogens isolated. Hemophilus influenza and Moraxella come up second and third.

Now, with this question of what organisms are isolated from patients who have been treated and failed therapy we see that there is a difference between studies that are reporting data from the 1980s and before and those reporting in the 1990s, and fundamentally what we see is that in the 1980s beta-lactamase producing organisms, Hemophilus influenzae or Moraxella were the most likely organisms to be isolated from patients who failed therapy.

Here we see drug-resistant Strep limo(?) and there are some intermediate resistant strains reported but those would likely be different than some of the strains down here in the 1990s where we start to see much higher rates of truly resistant Streptococcus pneumoniae presenting and a fairly stable picture with regard to Hemophilus and Moraxella.

One of the studies that I just alluded to was from Kentucky in the mid-nineties and actually on the prior slide may have been misreported, but here is an example of pathogens isolated from the middle ear after a few days of antibiotic exposure that is those who are failing therapy, those who are symptomatic at approximately 2 to 3 days and therefore being re-evaluated with a tympanocentesis and we can see that overwhelmingly Pneumococcus is the organism that is isolated in that setting, that beta-lactamase producing organisms count for only 11 percent of the isolates in this study from Kentucky.

What about the issue of self-resolution? The classic study here is Harry's study from Alabama in the 1960s and his data show that Pneumococcus actually only infrequently resolves by itself within 3 to 6 days. Hemophilus resolves by itself about half the time. Moraxella more recent estimates suggest probably resolves by itself 70 or 80 percent of the time.

So, we see that Pneumococcus here is the on least likely to resolve by itself.

Are there different clinical syndromes associated with these different pathogens, that is to say are some more likely to be severe than others and should those

perhaps be the focus of our therapy?

Rodriguez and Schwartz in the Washington, DC area studied 224 episodes, evaluated with tympanocentesis and clinical scoring, and they found that a characteristic of a proportion of isolates that were found, that is Pneumococcus No. 1, Hemophilus No. 2, Moraxella No. 3. They found interestingly that if you look at the patients with more severe presentation, that is fever greater than 38.3 with either red or yellow bulging tympanic membrane that 41 percent of the cases of Streptococcus pneumoniae fit into this category. Only 1.6 percent of those caused by H. flu and only 2 percent of those caused by Moraxella fit into this category of bulging TM with fever giving actually a positive predictive value of this clinical syndrome of 94 percent for etiology by Streptococcus pneumoniae.

There is no difference in that study in pain score. However, Harry, also, did a study like this back in the sixties, 858 episodes evaluated by tympanocentesis and clinical findings at presentation, found that 34 percent of the patients' middle ear fluids grew Streptococcus pneumoniae, 20 percent middle ear fluids grew Hemophilus. Severe pain was seen in 41 percent of those with Streptococcus pneumoniae versus 17 percent of those with H. flu, fever over 101 in 30 percent with Strep. pneumonia, 13

percent with H. flu, severe pain and temperature greater than 101, 12 percent of Strep. pneumo and only .6 percent of those with H. flu and mild or no pain and a temperature less than 100, 13 percent with Strep. pneumo, 26 percent with H. flu.

So, it is pretty clear evidence that these two organisms while certainly overlapping Hemophilus was more of a pest than a real pathogen in this disease.

Just more evidence supporting the idea that these organisms produce different syndromes comes from evaluating inflammatory mediators. This is IL6 isolated from middle ear fluid by pathogen. Streptococcus pneumoniae is in this first column, Hemophilus influenzae here and Moraxella catarrhalis here. You see clear evidence that higher rates of inflammatory mediators are seen with Streptococcus pneumoniae than the other two organisms.

In fact, in animal studies with Hemophilus influenzae it has been shown the peak of inflammatory mediator with this particular organism occurs before clinical symptoms can be detected, that is the inflammation is already resolving at the time that clinical symptoms are apparent.

Perhaps the major reason that we can justify treating acute otitis media is the prevention of

suppurative complications. The treatment of otitis certainly can have some effect on pain, but that is more evident in those with severe disease than with mild disease as Dr.Marchant showed us with mild disease when used to treat 25 people who are going to actually benefit from therapy, but with suppurative complications as a consideration perhaps treatment can be justified.

Pneumococcus if we look at the most common or most severe and important of the suppurative complications of acute otitis media is acute mastoiditis and this is the rank order of pathogens with regard to their rates of isolation in acute mastoiditis. Pneumococcus is No. 1 in virtually every study reported around the world in the last 20 years. Drug-resistant Streptococcus pneumoniae is being increasingly reported in many of these studies although there are some studies that show while Pneumococcus is No. 1 that the rate of pneumococcal resistance is not going up quite as fast as we feared.

Group A Streptococcus interestingly has replaced Hemophilus influenzae as the No. 2 pathogen, remarkable because it is really the No. 4 on the list of causes of acute otitis media. Staphylococcus aureus and Pseudomonas come in in the three and four slots reflecting probably more chronic disease than truly acute, but I think what is

notable is that Hemophilus influenzae is reported most often as not occurring at all or in studies that are done looking at children in the 1970s and 1980s up to about 5 percent.

One of the interesting points here, however, is that in the seventies and eighties we were not using the Hemophilus influenzae B vaccine and very few of these studies differentiate the Hemophilus influenzae that they report as being either typable Type B or non-typable disease.

There are occasional reports of non-typable H. flu as an etiologic agent but they are really quite rare. To my knowledge Moraxella catarrhalis has not been reported as a cause of mastoiditis at all. In summary, Pneumococcus i clearly the major focus if we are worried about suppurative complications of otitis media and Hemophilus influenzae is literally reportable as an etiology.

If we consider then that Streptococcus pneumoniae is behaving as suppurative pathogen in this disease acute otitis media what is different about Hemophilus? It is an organism that commonly colonizes the nasopharynx. So it is present in children normally in the day care age group. It is typically thought the non-typable H. flu as opposed to type B. It is typically thought to lack the ability to

invade in normal hosts. It is almost never the cause of bacteremia or meningitis for example.

H. flu otitis is more likely to follow viral infection than any other bacterial organism and therefore giving the impression that perhaps even more than with the other organisms it requires some viral infection to damage the host before Hemophilus can impose disease, again, a similar point here that otitis prone children are more likely to be colonized with H. flu reflecting again the fact that Hemophilus influenzae is the No. 1 pathogen associated with otitis media with effusion as opposed to acute otitis media, and as we ponder this, along with some recent data looking at the role of Hemophilus for example in bronchitis, chronic bronchitis, its ability to attach to non-ciliated epithelial cells and to macrophages and remain viable may explain some of the role of this organism in both otitis media and other diseases, and a question comes up whether its intracellular location shields it from some antibiotic therapy or whether simply the fact that it is part of a virtual biofilm relatively metabolically inactive allows it to escape complete eradication and then recur.

In summary if we look at the relative importance of these two major pathogens in acute otitis media since Streptococcus pneumoniae is the No. 1 isolate occurring 30

to 50 percent of bacterial isolates, Hemophilus influenzae the No. 2, 15 to 30 percent in the US, Streptococcus pneumoniae is the No. 1 cause of treatment failure in the 1990s, Hemophilus the No. 2 cause. The rates of drug resistant Strep pneumo are rising faster than the rates of beta-lactamase positive Hemophilus influenzae. Strep pneumo fails to resolve on its own without appropriate antibiotic therapy about 80 percent of the time versus 50 percent of the time for Hemophilus. Streptococcus pneumoniae is associated with a severe acute otitis media syndrome versus a less severe syndrome for Hemophilus and more of a chronic otitis media with effusion syndrome. Streptococcus pneumoniae is an invasive pathogen with the potential to do real damage and long-term morbidity whereas Hemophilus influenzae is a non-invasive opportunist which may cause temporary morbidity and there are virtually no suppurative complications other than an occasion perforated tympanic membrane associated with Hemophilus influenzae in the normal host, and this organism is more likely to recur after therapy.

Thank you.

DR. DUNNE: Thank you, Dr. O'Rourke.

Why should physicians choose to use azithromycin for treatment of acute otitis media? First, it is

bactericidal against the pathogens responsible for this disease. It has a pharmacokinetic profile suited for the treatment of infection. It reaches effective concentrations in the middle ear. It is used to sustain concentrations in white blood cells. A complete course of therapy can be given in a single dose and shorter courses of therapy will optimize compliance.

Azithromycin is a well-tolerated antibiotic. The side effects have been well described and are generally gastrointestinal in nature. It is recommended in treatment of children who are penicillin allergic and post approval the oral suspension has been prescribed over 40 million times.

Clinical efficacy equivalent to comparators has been demonstrated first with the 5-day dosing regimen and now extended to 3-day and single-dose therapies.

The single-dose therapy though has additional features of interest. Giving the dose all at once allow for higher peak drug levels earlier in the course of infection. As azithromycin concentrates in white blood cells delivery of the regimen early in the course of therapy takes advantage of the period of maximum neutrophil recruitment to the site of infection. Based on in vitro data entry into white blood cells, uptake per se is increased with

elevated temperatures. The single dose maximizes the rate of compliance and minimizes the burden on the care giver.

The focus of today's presentation will be around the pivotal clinical trials that support the use of the single and 3-day dose for treatment of acute otitis media. Before we get to that data, however, we will briefly review some relevant preclinical information.

The development program that generated azithromycin was focused on finding a macrolide that was more acid stable than erythromycin.

That goal was achieved by insertion of a nitrogen into the macrolide ring. The consequence of this nitrogen insertion was to add a second basic site to the compound and it is the positive charge at these two sites here and here that is responsible for the propensity of azithromycin to accumulate within cells.

At extracellular pH a small percentage of the compound exists in a neutral form here. This neutral form is more easily able to traffic through cell membranes.

Once exposed to the lower pH in acidified vacuoles more of the drug becomes proteinated leading to accumulation within this space here. This accumulation within cells that have acidified vacuoles such as neutrophils and monocytes is important in a disease such as

acute otitis media, given the infiltration of these cells into the middle ear during the course of infection.

This is an H&E stain of a cross section of the mucosa of infected middle ear. The lumen is here. The mucosa down here.

One can see the infiltration into the mucosa by neutrophils. Presumably it is through this infiltration to the middle ear space by neutrophils that azithromycin is delivered to the site of infection.

It is, also of interest to note the extent of the tissue involvement in this disease process. Evidence that azithromycin accumulates within the middle ear space comes from a number of pharmacokinetic studies in which levels were measured within the middle ear.

In the study by Skaglione, this top study here one can see that the distribution between cells in the extracellular compartment is similar within the middle ear space to what we see in the blood.

In general these levels exceed the MICs for sensitive pathogens responsible or acute otitis media. The in vitro microbiologic profile of azithromycin has been extensively looked at over the last 10 years.

In a recently published study the MIC 90 to Streptococcus pneumoniae for over 4000 organisms was found

to be 2 micrograms per ml.

Similarly in over 3000 isolates of Hemophilus influenzae the MIC 90 was 2 micrograms per ml. For Moraxella catarrhalis the MIC 90 was found to be less than 0.12 micrograms per ml.

While MIC 90 for Moraxella and Hemophilus has not changed over the last 10 years the MIC 90 for Streptococcus pneumoniae has been increasing. There are two major mechanisms of resistance used by Streptococcus pneumoniae against macrolides. The first works through an efflux pump. The MIC 90 for 70 isolates of Streptococcus pneumoniae harbored in a FA efflux pump was found to be 8 micrograms per ml.

The other mechanism is coded by an erm(?) d-methylase. Among 65 strains carrying the resistance mechanism for erm-d-methylase, among 65 strains carrying the resistance mechanism for erm-d-methylase the MIC 90 was greater than 128 micrograms per ml.

There has been identified an association between resistance to penicillin and resistance to macrolides. Among 1200 isolates of Streptococcus pneumoniae susceptible to penicillin the MIC 90 to macrolides was 0.25 micrograms per ml.

Among isolates with high-level penicillin

resistance the MIC for macrolides increases to 32 micrograms per ml.

Presented here is similar information examined in a different manner. Among isolates susceptible to penicillin only about 3 percent were found to be resistant to erythromycin. For isolates demonstrating high level resistance to penicillin as many as 61 percent were found to be resistant.

The phenomenon of cross resistance is seen across other antibiotics including another beta-lactams F-furoxine(?) trimethaprim(?) sulfa and to a lesser extent with tetracycline.

This list of antimicrobials, also, tracks with age such that isolates obtained from younger children are more likely to be resistant than those obtained from those over the age of 13. For example, 63 percent of isolates obtained from children under the age of 2 were susceptible to erythromycin in this series compared to 80 percent with isolates takes from those over the age of 13.

Resistance to antimicrobials including macrolides has been increasing over the last 10 years. Presented here are data from eight published surveillance studies examining pneumococcal resistance to either macrolides or penicillin, and the penicillin break points are given here

in these studies. These red squares here are non-susceptible isolates. The green squares are those that are high-level resistant.

In 2001 in vitro resistance to macrolides is seen in up to 25 percent of isolates with high-level resistance to penicillin in up to 20 percent.

In general macrolide resistance in the US has been associated with the efflux pump mechanism.

These isolates were obtained from a variety of sources. So a range of resistance rates can be seen in any one year surveyed. Generally resistance to community-acquired respiratory tract isolates is higher than that obtained from steroid sites.

Now, focusing on susceptible isolates, in vitro experiments demonstrate bactericidal activity of azithromycin against Pneumococcus.

In this time kill experiment Streptococcus pneumoniae is exposed to azithromycin at 2 and 8 times the MIC. After 24 hours of incubation there has been a 3 to 6 log reduction in the quantity of organisms in culture consistent with a bactericidal effect.

Similarly bactericidal activity has been seen for azithromycin against Hemophilus. In this time kill experiment Hemophilus influenza is exposed to azithromycin

at the MIC and at 4 times the MIC. After 24 hours in incubation there has been a 4 and 6 log reduction in the quantity of organisms in culture again consistent with bactericidal activity.

We now move to in vivo data derived from animal models, specifically the chinchilla model of acute otitis media. In this experiment presented at ICAC last year by Franz Bable from Steve Pelton's group chinchillas are infected with non-typable Hemophilus influenzae.

Starting 2 to 4 days later they undergo tympanoscopy as well as tympanocentesis at various time points with bacterial cultures as well as drug levels.

Dosing is started on day zero with either 30 milligrams per kilo or 120 milligrams per kilo orally each day for 5 days.

Drug levels from the middle ear are presented here. Peak levels are seen at day 5. Total middle ear fluid levels which would include any intracellular as well as extracellular drug are 9.6 micrograms per ml on the 120 milligram per kilo dose and approximately 3 micrograms per ml on the 30 milligrams per kilo dose.

These total middle ear fluid concentrations are within the range of levels obtained from children getting a 30 milligram per kilo dose. The extracellular levels from a

30 milligrams per dose are lower than that of the total levels you can see here. These are the extracellular levels. These are the total levels,

Not shown here the serum levels seem with the 30-milligram-per-kilo dose most closely to approximate the serum levels seen with a 30-milligram-per-kilo dose given in children.

Quantitative bacterial cultures from the middle ear were performed. One can see it on day 3 no significant reduction in bacterial counts was observed compared to controls. By day 5 the mean counts on the 30-milligram-per-kilo dose were approximately 2 logs lower than control while those from the 120-milligram-per-kilo dose were 5 logs lower.

Bacterial eradication continued through day 11. Between this slide and the next one there are three points to be made. The first is that at doses at least in the range of what could be seen in children there is a significant antimicrobial effect of azithromycin against Hemophilus influenzae and that effect is observed as a dose response.

The other two points focus on methodology. The second point is that the timing of the culture significantly affects the impression of antimicrobial

effect. For example, if day 3 in this experiment was the only time point looked at one could conclude that neither regimen has activity.

In contrast at day 5 one could conclude that the 120-milligram-per-kilo dose is very potent and the 30-milligram-per-kilo dose while not fully clearing the infection has been effective enough to reduce the concentration of organisms by 2 logs.

The third point to be made is done by contrasting these findings with an analysis of the same data looked at in a qualitative fashion. Here is the same information on antimicrobial effects. It is reported as cultures being either positive or negative. Now, one could interpret the day 5 data as reflective of a 50 percent failure rate for the 120-milligram-per-kilo dose and a 95 percent failure rate for the 30-milligram-per-kilo dose, a very different picture of antimicrobial activity from what was previously demonstrated.

So, the sensitivity of the test methodology must be considered in forming an interpretation of antimicrobial activity in these kinds of settings.

We turn now to the clinical program where we will start with an overview of the data at the point of use of azithromycin as a 30-milligram-per-kilo dose now given over

5 days, a 5-day regimen.

These were the pivotal studies that supported the 5-day program. In the two comparative studies patients given azithromycin had a clinical cure rate similar to the children taking the comparative agent. There were two studies that identified pathogens at baseline.

The clinical success rate at day 30 for the 56 children with Streptococcus pneumoniae identified at baseline was 71 percent. With 47 with Hemophilus influenzae identified at baseline it was 64 percent and for the 26 children with Moraxella catarrhalis it was 73 percent. The results of the smaller comparative study were similar.

Of the 975 patients who received azithromycin 7.2 percent developed an adverse event related to drug compared with 23 percent of the 827 children who received amoxicillin/clavulanate. The most common adverse event seen was diarrhea at 12.6 percent for children getting amoxicillin and clavulanate; vomiting and abdominal pain were also seen.

We will come back to these side effects later when we compare them to the shorter courses of therapy with azithromycin.

Based on the animal experiments and pharmacokinetic properties of azithromycin it appeared that

the total dose and not the duration of dosing might be most relevant to treatment outcome. Given this background and the ongoing medical need for therapies which could improve compliance rates we undertook a program to reduce the dosing duration for treatment of acute otitis media to under 3 days and then to a single dose therapy.

I would just like to point out that the regulatory implications of this program were not to gain an indication for acute otitis media as that was previously established with the 5-day program but rather to adjust the dosage and administration section of the label to allow for 5, 3 or 1 day of dosing.

Now, for orientation the actual daily dosing of these regimens is provided here. The 5-day dosing regimen is given at 10 milligrams per kilo on the first day and 5 milligrams per kilo each day from days 2 to 5.

The 3-day dosing regimen as given as 10 milligrams per kilo each day for 3 days and the single dose regimen provides the entire 30-milligram-per-kilo dose in a single administration.

The program to study these shorter dosing regimens follows the 1998 FDA guidance on the design of studies for acute otitis media. These guidelines require one statistically adequate comparative study with clinical

end points and a test of cure visit 2 to 4 weeks after conclusion of therapy.

In addition there should be one non-comparative trial with tympanocentesis at baseline to identify pathogens of interest and clinical cure rates for these pathogens should be clinically acceptable to find as comparable to a labeled comparator drug.

The program had pivotal and supportive studies. The pivotal studies in support of the single-dose program were study R-0581, a double-blind randomized comparative clinical trial and study 1015, a non-comparative study with tympanocentesis at baseline.

There was one comparative double-blind randomized clinical trial in support of the 3-day dosing. It was agreed that microbiologic data from the single dose program could support the 3-day program given the data already available from 5-day dosing.

There was one Phase II supportive trial that served as a pilot study and it compared azithromycin as a single-dose therapy with 3 days of dosing with azithromycin with ceftriaxone given intramuscularly. Patients had a baseline tympanocentesis in this study as well.

We will start by reviewing the single-dose program. The best place to start to understand

comparability between all the studies in this single dose program is to look at who was included in the trials. We will do that by reviewing the inclusion and exclusion criteria for the single-dose program overall.

Now, this is a busy slide, but I will draw your attention to the most important points. First you will see that there are four columns at the top. The three columns on this side are the pivotal studies in the program. This column provides a reference point for the 1998 FDA guidance specifically in this slide on the symptoms consistent with acute otitis media.

All three studies allowed for enrollment of children down to 6 months of age. Ninety-eight percent of the children in study 1015 had either ear pain or fullness. Seventy-seven percent of the children in R-0581 had ear pain. Ninety-three percent had either ear pain or a history of fever and 96 percent of the children had ear pain in study 95001. So, all of these children appear to have symptoms consistent with acute disease.

Presented here are the inclusion criteria for signs of tympanic membrane disease. Over 90 percent of the patients had at least one abnormality in study 1015. The majority had more than one. All patients in both 1015 and R-0581 were to undergo electroacoustic reflectometry and

have acoustic gradient angle of less than 70.

Ninety-nine percent of those in R-0581 and 87 percent of the children in 1015 had that finding. The majority of the remaining children in 1015 had a perforated eardrum. So, they couldn't undergo that test. All of the children in 95-001 had a bulging eardrum at entry.

Recent antibiotic use was exclusionary in each study. Though not specifically indicated in every protocol no child was enrolled with typanostomy tubes present or who had otitis externa.

The primary end point was clinical cure. The primary time point for test of cure was day 28. In addition to cure and failure the assessment of improvement at day 28 was collected in study R-0581 and 95-001. As a result the comparison of clinical success which is the sum of cure plus improved was, also, analyzed for these studies at the day 28 time point. This clinical success assessment was made at the end of therapy visit in all the studies and is examined as a secondary end point.

The population of patients analyzed for clinical efficacy at day 28 included patients who took at least one dose of study medication, had a diagnosis of acute otitis media and returned for a visit at day 28.

Anyone who received a concomitant antibiotic for

failure was carried forward as a failure. The population evaluated for bacteriologic response included all the clinical efficacy population who also had a pathogen of interest isolated at baseline.

The assessment of cure was defined as complete resolution of specific signs and symptoms of acute otitis media. Following recent guidance for the two more recent studies, 1015 and R-0581 the presence of a middle ear effusion per se did not preclude an assessment of cure. So, some residual signs of effusion did not prevent the investigator from calling that patient a cure.

So, we will focus on the pilot study first. Study 95-001 was the first study designed to assess the activity of azithromycin given as a single dose for the treatment of acute otitis media. It compared the single-dose regiment with azithromycin given for 3 days with ceftriaxone. This was a prospective single center study performed in Costa Rica. The patients were screened and randomized to azithromycin as either a single dose or a 3-day dose or to ceftriaxone. Each of the azithromycin regimens was given with a placebo oral suspension to match the other.

Ceftriaxone was given intramuscularly at 50 milligrams per kilo as a single administration. There was no blinding for ceftriaxone as it was not felt appropriate

to give placebo injections to the other groups.

In an attempt to blind this regimen though the physician assessing the clinical response did not administer the study drugs.

Typanocentesis was performed at baseline. Follow-up occurred at typical intervals through day 28.

Sixty-six children were randomized to each regimen. All of these children were available for a safety assessment and all but three were included in an assessment of efficacy at day 28. Approximately one-half of the children had no organism identified at baseline.

The mean age of children enrolled was 2.4 years and roughly 40 percent were under the age of 2. The distribution of demographic characteristics was comparable among the treatment regimens.

The mean duration of symptoms of acute otitis media prior to randomization was 1.5 days for those given azithromycin as a single dose, 2.4 days for those given a 3-day dose of azithromycin and 1.7 days for those given ceftriaxone.

Analgesics or antipyretics were used during the course of the study to a similar extent by children on each regimen. Symptomatic medications for respiratory tract infections were infrequently used throughout the

observation period. The clinical success rate at day 14 was similar on each regimen as you can see here.

At day 28, again, there were similar success rates and cure rates, success on this line, cure here. Provided for reference is the 95 percent confidence interval on the difference in outcome between the single dose azithromycin and ceftriaxone.

Clinical outcome was, also, stratified by age. Clinical cure rates at day 28 were similar between regimens for each group. As is typically seen the cure rates for children less than the age of 2 are lower than those for children over the age of 2.

Fifty-seven of the 60 Streptococcus pneumoniae isolates obtained during the study had susceptibility testing performed. Forty-six of those were susceptible to azithromycin and 11 were resistant. All isolates were susceptible to ceftriaxone.

All isolates of Moraxella catarrhalis and Hemophilus influenzae were susceptible to both azithromycin and ceftriaxone. Of patients in whom Streptococcus pneumoniae was identified at baseline the clinical cure rate at day 28 was 85 percent in the 20 patients receiving a single dose of azithromycin, 94 percent for the 17 patients receiving 3 days of azithromycin and 83 percent

for the 23 children receiving ceftriaxone.

Of patients for whom Hemophilus influenzae was identified the cure rate was 88 percent in the eight patients receiving a single dose, 69 percent in the 13 patients receiving 3 days of azithromycin and 89 percent in the nine children receiving ceftriaxone. There were only two patients where the Moraxella catarrhalis was identified.

Coming now to safety, 11 percent of children given a single dose treatment of azithromycin had a treatment-related adverse event compared with 9 percent of those given 3 days of azithromycin and 9 percent of those given ceftriaxone.

Similar rates of diarrhea were seen on each treatment regimen with rash more common in the ceftriaxone-treated group and vomiting at 5 percent more common with the single-dose therapy with azithromycin.

There had been a concern that giving the entire dose of azithromycin all at once would result in an unacceptable GI side effect profile. The adverse event rate seen here though was encouraging and supported the clinical development program for single-dose therapy.

We turn now to study R-0581. This study was designed to collect comparative clinical data for the

single-dose regimen. It was a multicenter randomized double-blind comparative study of azithromycin given at a single dose and amoxicillin/clavulanate each with matching placebos.

A history and physical exam was performed at baseline. The first dose of study medication was given in the clinic and patients were asked to wait for 30 minutes. Any patient who vomited during that time was redosed. Patients were contacted by phone between days 3 and 5 at which time data relevant to adverse events, compliance and clinical symptoms was collected.

At days 12 to 16 and again at days 28 to 32 patients returned to the clinic where data relevant to adverse events and clinical response was obtained.

One hundred and seventy-five patients were randomized to each study regimen and 173 in each group had a safety assessment. One hundred and fifty-one patients treated with azithromycin and 154 treated with amoxicillin/clavulanate were included in the efficacy analysis at day 28.

The mean age of children randomized to azithromycin was 2.7 years and to amoxicillin/clavulanate it was 3.4 years. Approximately 40 percent of the children enrolled were under the age of 2.

Regimens were balanced with respect to age, gender and race. The duration of symptoms of acute otitis media prior to randomization was 3.4 days for those given azithromycin and 3.9 days for those given amoxicillin/clavulanate.

Approximately 80 percent of the children had a prior history of acute otitis media. Analgesics and symptomatic medications for treatment of a respiratory tract infection were used during the course of the study to a similar extent by patients one each study regimen.

The clinical success rate at day 14 was similar on each treatment regimen as seen here. The clinical success rates at day 28 were, also, similar with a lower limit on the 95 percent confidence interval on the difference of minus 10 percent given here. The lower limit on the difference in cure rates was minus 7 percent.

Clinical outcome stratified by age was, also, examined. The cure rates at day 28 for children above or below the age of 2 were similar for each regimen. Again, as expected cure rates for children under the age of 2 were lower than for those children older than 2.

Ninety-nine percent of children randomized to azithromycin took their study medication compared to 83 percent of those amoxicillin/clavulanate.

Turning again to safety 17 percent of the children receiving a single dose of azithromycin reported an adverse event related to drug compared to 23 percent of those randomized to amoxicillin/clavulanate.

Diarrhea and rash were seen more frequently in children given amoxicillin/clavulanate and vomiting was seen in 4 percent of children on either regimen.

Study R-0581 confirmed and extended the efficacy of a single dose as we had seen previously in the pilot study. We will now review study 1015.

Study 1015 was designed to obtain clinical outcome information according to the pathogen isolated by tympanocentesis at baseline. It was a prospective open-label multicenter non-comparative trial.

History, physical exam and tympanocentesis were performed at baseline. The first dose of study medication was given in a clinic and patients were asked to wait for 30 minutes. Any patient who vomited during that time was redosed.

Patients were contacted by phone at day 5 at which time data relevant to adverse events was collected. At day 10 and again at days 24 to 28 patients returned to the clinic where data relevant to adverse events and clinical response was obtained. The primary efficacy end

point was clinical cure at day 28 by baseline pathogen.

Organisms isolated by the local laboratory were sent to a central lab for confirmation. Two hundred and forty-eight patients were enrolled in the study and all of these were included in safety assessments. Two hundred and forty-two patients were assessed for clinical outcome at day 28. Approximately one-half of the patients had an organism identified at baseline.

The mean age of children enrolled in the study was 3.4 years. Thirty-five percent of those enrolled were under the age of 2. The mean duration of symptoms of acute otitis media was 2.5 days and 72 percent of the children had at least one previous episode of acute otitis media.

Analgesics were used during the course of study in 63 percent of the children and symptomatic therapies for respiratory tract infections were used in 19 percent.

The clinical success rate at day 10 was 89 percent. The clinical cure rate at day 28 was 85 percent. This is all patients enrolled. The clinical cure rate for children over the age of 2 was 89 percent and it was 77 percent for those under the age of 2. Again, we see that children under the age of 2 had a lower success rate than the older children.

Eighty-eight percent of 76 children with

Streptococcus pneumoniae isolated at baseline were cured at day 28. Sixty-four percent of 44 children with Hemophilus influenzae isolated at baseline were cured at day 28 and all 10 patients with Moraxella catarrhalis were cured.

I would like to focus a little bit more on the isolates of Streptococcus pneumoniae identified in the study.

Of 76 patients with Streptococcus pneumoniae identified at baseline 67 isolates had susceptibility testing performed. Presented here is the number of isolates distributed by the baseline MIC.

The break point for resistance to azithromycin is 0.5 micrograms per ml which would make these 12 isolates resistant.

The resistant isolates sort into two groups, those with an MIC of 8 and those with an MIC of greater than 256 micrograms per ml.

We have some additional data on this group of 12 organisms. There were seven isolates that had an MIC of 8 micrograms per ml. All of these were susceptible to clindamycin and all had the mef-A gene identified by PCR, both characteristics of organisms that have an efflux pump mechanism of resistance.

All five of the isolates with an MIC greater than

256 micrograms per ml were resistant to clindamycin and had the erm B gene identified consistent with ribosomal resistance.

Presented here is the clinical outcome by baseline MIC for 66 patients that had clinical outcome data available. Four of the 12 patients with these resistant isolates failed therapy. You can see there are four right here. We did note that this child here had a resistant isolate recovered on therapy. So, I would, also, like to review this one patient.

This is an outline of the patient's clinical course. He presented with an abnormal reflectometry score in the left ear and tympanocentesis of that ear revealed Hemophilus influenzae and Strep. pneumoniae with an MIC of 8.

On day 4 because of persistent symptoms he came back to the clinic where the left ear had improved. However, the right ear was now found to be involved. Tympanocentesis and culture of that ear revealed Streptococcus pneumoniae but now the MIC was greater than 256 micrograms per ml. The child's therapy was then switched.

In order to determine if this was the same organism, this Streptococcus pneumoniae was the same or not

but simply had a higher MIC we did pulsed field gel electrophoresis on these two isolates and that is presented here. This is the strain an MIC of eight. This is the strain with an MIC of greater than 256 micrograms per ml, and these two strains of Strep. pneumoniae were determined to be clonally distinct which raises the possibility that the child's failure on therapy was a consequence of a superinfection with a less-sensitive organism. Because of the cross resistance seen between penicillins and macrolides in Strep. pneumoniae we performed an assessment of clinical outcome by baseline penicillin susceptibility.

Forty of the 65 isolates were susceptible to penicillin as shown in the top left of the table, these 40 over here. Thirty-eight of the 40, 95 percent were assessed as cured at day 28.

Just to note all of these 40 isolates were, also, susceptible to azithromycin. Here in the left-hand column on this side there are 16 isolates with intermediate resistance and 12 of the patients with these isolates were clinically cured.

In the middle nine isolates demonstrated high-level resistance to penicillin and six of the patients with these isolates were clinically cured.

I would like to focus some more attention on

these nine isolates now in the next slide.

These nine isolates were analyzed according to their macrolide susceptibility as seen in the bottom table there. Three of the isolates were susceptible to azithromycin and all three of the patients with those isolates were clinically cured.

An interesting thing to note here is that all of the isolates with the erm B phenotype demonstrated high-level resistance to penicillin. So, there was a complete correlation between those two.

Now, I should, also, note that these data are updated from what you have in your briefing document on Page 25. Now, safety. In this non-comparative study 12 percent of patients receiving azithromycin experienced a treatment-related adverse event. The most frequently identified event was vomiting seen in 6 percent of the patients. In this study of single dose of azithromycin the clinical outcome assessed in patients with infections due to the key pathogens responsible for acute otitis media was comparable to that seen with the 5-day regimen.

Okay, so now we will move from the single dose program to the 3-day program, and we will start with study 1014. The purpose of this study was to collect comparative data on the activity of azithromycin given over 3 days for

treatment of acute otitis media.

This was a randomized double-blind multicenter study where patients were given either azithromycin for 3 days or amoxicillin/clavulanate at 45 milligrams per kilo per day divided b.i.d. for 10 days with matching placebo.

Children were enrolled down to the age of 6 months. Ninety-seven percent of the children had either ear pain or fullness. The majority of subjects had more than one of the typical signs of tympanic membrane disease. Ninety-eight percent of the patients had an electroacoustic reflectometry exam with an acoustic gradient angle less than 70 at baseline..

Recent antibiotic use and the presence of tympanotomy tubes were exclusionary criteria and no child was enrolled with otitis externa.

A history and physical exam was performed at baseline. Patients were contacted by phone at day 3 to 5 at which time adverse event data and compliance data were collected.

At day 10 and again at day 24 to 28 patients returned to the clinic where data relevant to adverse events and clinical response was obtained.

The primary end point was clinical cure. The primary time point was day 28 at which time a clinical

assessment of cure or failure was obtained. Clinical efficacy at day 28 was analyzed for patients who took at least one dose of study medication, had a diagnosis of acute otitis media at baseline and returned for that visit.

Patients who used a concomitant antibiotic for failure were counted as failures and carried forward as such.

Cure was defined as complete resolution of the signs and symptoms of acute otitis media. The presence of a middle ear effusion would not necessarily preclude an assessment of cure.

One hundred and eighty-eight children were randomized to azithromycin and 185 to amoxicillin/clavulanate. All of these children were included in the safety analysis. One hundred and eight-two children given azithromycin and 180 given amoxicillin/clavulanate were included in the efficacy analyses at day 28. Symptoms prior to enrollment for children on either regimen was 1.2 days. Over 80 percent of the children had a previous episode of acute otitis media.

Analgesics were used by approximately half of the children on either regimen at any time during the study and 40 percent used symptomatic treatments for respiratory tract infections.

Clinical success rate at day 10 was similar on each regimen given here. Clinical cure rates at day 28 were equivalent with a lower limit of the 95 percent confidence interval on the difference of minus 5.

Clinical outcome stratified by age was, also, examined. The cure rate at day 28 for children above or below the age of 2 was similar on each regimen. Again, as expected cure rates for children under the age of 2 were lower than for children over the age of 2..

Ninety-nine percent of children assigned to azithromycin completed their treatment regimen compared to 89 percent of those given amoxicillin/clavulanate.

Eleven percent of children taking a 3-day regimen of azithromycin had a treatment-related adverse event compared to 20 percent of those taking amoxicillin/clavulanate.

Diarrhea and rash were seen most frequently in those on amoxicillin/clavulanate. Vomiting was seen to a similar degree on each regimen.

In this comparative study the 3-day regimen of azithromycin demonstrated comparable safety and efficacy to amoxicillin clavulanate.

I would like now to present a summary overview of the four studies that I just presented. As we have seen in

the three comparative studies azithromycin was demonstrated to be as effective as the comparator as defined by the lower limit of the confidence bounds and the difference in cure rates.

The similarity in efficacy rates was, also, seen in the more difficult-to-treat subpopulation of children under the age of 2 and the same conclusion can be drawn from an assessment in this subpopulation at the earlier end-of-therapy time point.

An 88 percent clinical cure rate was seen in the 76 children from whom Streptococcus pneumoniae was isolated at baseline, a 64 percent cure rate in the 44 children from whom Hemophilus was identified at baseline and all of the children from whom Moraxella was identified.

Similar results were seen in the smaller comparative study. Presented here are safety data from the comparative pivotal studies for the single and 3-dose regimens as well as the 5-day regimen submitted in the original application.

The comparators have been pooled across all the studies. Treatment-related adverse events were seen in 14 percent of patients given a single dose of azithromycin, 10 percent of those given the 3-day dose and 8 percent of those given the 5-day dose. This compares to a 22 percent

adverse event rate in those given the comparator drug.

Diarrhea was the most frequently observed in the comparator regimen. Vomiting was seen in 1 percent of those given the 5-day regimen here, 2 percent of those who got the 3-day regimen, 5 percent of those who got the single-dose regimen and 4 percent of those who got the comparator.

Now, there is a progressively higher rate of patients with adverse events in the 30-milligram-per-kilo dose of azithromycin as the duration of dosing shortens.

This was not unanticipated. The gastrointestinal side effects are dose proportional and the 30-milligram-per-kilo dose on day one with the single-dose therapy delivers more drug than the 10-milligram-per-kilo dose on that same day, but given the shorter duration of dosing on the single dose the likelihood of experiencing related adverse events on subsequent days would decrease. Therefore we thought it was, also, important to consider not just the number of patients with adverse events but the actual number of adverse events accounting for the duration of each event as well.

For reference we see the total number of patients that had an adverse event here. You saw that in the previous slide.

Noted below, however, are the number of related

adverse events normalized for patient year of exposure. What one sees is that while more patients getting the single dose had a side effect, mostly on the first day of dosing, the number of event days of side effects was not higher than on the other regimens.

In review of the clinical data there are a few topics that were of additional interest to us and merit some further discussion.

These topics include the effect of vomiting on day 1 on the clinical outcome of children assigned to the single-dose therapy, a comparison of outcome at day 28 for published studies and empiric therapy with acute otitis media with azithromycin as well as a by-pathogen outcome assessment at day 28 and a look at outcomes at earlier time points than day 28, including the use of other measures to assess clinical response.

We wanted to assure ourselves that there was no negative impact on clinical outcome for patients assigned to the single-dose therapy who subsequently vomited. A total of 52 children, 10.7 percent assigned to single-dose therapy vomited at some point during the observation period which goes out to 30 or 35 days after dosing.

Thirty-six of these children vomited on the first day. So, there may be concern about vomiting around the

time of dosing on this first day. We assessed outcome for those 36 children and compared that outcome to the group that did not vomit on that day. Ninety-one percent of the children who vomited were cured or improved at day 14 compared to 89 percent of those who did not. At day 28 the rates were 85 percent and 81 percent.

Based on this overall measure of clinical outcome at least of the patients in this program the children who vomited initially were not disadvantaged.

The previous data presented information on a population basis. The data presented here measure absorption on an individual patient basis and are taken from PK studies in normal adult volunteers given a single dose of 2 grams or 3 grams of different formulations of azithromycin, four formulations here in the first study, two formulations here, two formulations over here.

Displayed in the red triangles here are the mean AUC for each group with corresponding standard errors around it. The green triangles are individual results from patients who vomited greater than 2 hours after dosing, here, here, here and here and here, and the yellow from those who vomited within 2 hours. So, that would be these two, this one, these here, here, here.

The yellow triangles highlighted with purple dots

are those that vomited within 30 minutes. There are four of those, one, two, three, four.

One can see that the values for patients who vomited fall within the standard error and are as likely to be above the mean as below regardless of the timing of the vomiting post-dose.

These two sets of data provide some assurance that individuals that vomit around the time of dosing are as likely to be clinically cured as those who do not vomit.

We will now examine the clinical response at day 28 for any azithromycin comparative study of empiric therapy for acute otitis media and then look at the clinical outcome at day 28 for patients with either Streptococcus pneumoniae or Hemophilus identified at baseline who were treated with either azithromycin or any other approved therapy for acute otitis media.

Presented here are the 95 percent confidence intervals on the difference in cure rates for all studies either published or presented for regulatory review with outcome data available at day 28.

The studies in yellow here at the top are the two studies that supported the original 5-day dosing regimen. The study here, the 1014 study supports the 3-day dosing regimen. The study, R-0581 supports the single-dose regimen

and there are a variety of other published studies that have data available.

Now, in an analysis of studies that compared azithromycin to amoxicillin/clavulanate, so any one of these that had amoxicillin/clavulanate as the comparator totaled about 1800 patients, as well as an analysis of all of these studies with about 2000 patients.

The point estimate of difference in outcome is small, and there are very narrow confidence intervals around it.

Presented here is the 95 percent confidence interval on the point estimate of success. So, this isn't difference in cure rates now. This is just the point estimate of success for antibiotics that are approved for treatment of acute otitis media that have clinical outcomes data at day 28 for patients with Streptococcus pneumoniae identified at baseline.

The data is presented as clinical success. These here are clinical cure down here, and this is the as presented in the labels. For reference the outcome of patients given a single dose or azithromycin is given here. These vertical dashed lines just orient you around the upper or lower limits of the 95 percent confidence interval on that point estimate.

Now, some caution should be taken in interpreting these data. Important demographic variables like age, previous episodes of acute otitis media, other things that are important in outcome are not taken into account in looking at one drug versus another here.

These are simply the data as they appear in the label, but even so these are data that have been used for regulatory decisions and are available to treating physicians.

From these data the outcome at day 28 for children with acute otitis media due to Streptococcus pneumoniae and treated with a single dose of azithromycin is comparable to that of other regimens.

Presented here now are the 95 percent confidence intervals again on the point estimate of success for all drugs approved for treatment of acute otitis media that had data available in the product label on clinical outcome at day 28 in patients with Hemophilus identified at baseline.

The data is presented again as clinical success and clinical cure and again that is as shown in the labels.

For orientation this is the outcome of the single dose treatment here. The dashed lines are the upper and lower 95 percent confidence limits.

Again, no attempt is made to adjust the outcomes

by these other important demographic variables. This is just as it is.

Given that caveat it would appear that the clinical outcome at day 28 for children with Hemophilus at baseline treated with azithromycin is comparable to that of other approved therapies.

In addition to the information at the day 28 test of cure the data is collected throughout the observation period that may be, also useful in assessing clinical response. This would include various on-therapy data such as the use of additional antibiotics for failure, the use of analgesics or antipyretics to control symptoms and the results of questionnaires aimed at the patient's impression, the parents' impression I should say of clinical outcome.

Presented here is a survival-type analysis focusing on the time to use an additional antibiotic for failure. As a parent could bring a child to the clinic at any time for reassessment it provides an additional measure of the timing of clinical failure.

If I can draw your attention to the earliest time period here and actually looking over the whole curve as well you can see that there is no obvious difference in the time to antibiotic used for failure between any of the

regimens in this pooled analysis of the three comparative studies that I reviewed this morning.

Alternatively the earliest response to therapy could be measured by the use of medications to alleviate the symptoms of disease. Here I present the percentage of patients using analgesics throughout the observation period, in study R-0581 no difference in the use of analgesics was seen and the use of these symptomatic medications had dropped to 2 percent by about day 5.

Again, in study 1014 no difference in the use of these medications was seen suggesting that gross differences in the symptoms of acute otitis media among these regimens is unlikely.

In study R-0581 parents were asked at various intervals to assess how sick overall their child had been. One could see at day 3 to 5 here the parents felt that their children were improving at a similar rate between those given a single dose of azithromycin and those given 10 days of amoxicillin/clavulanate.

Following guidance documents the test of cure visit for this program occurred at day 28. Assessments of the day 10 to 14 end-of-therapy visit though were also performed.

Presented here are the 95 percent confidence

intervals on the difference in clinical outcome for all clinical trials comparing azithromycin to a beta-lactam that had an assessment of clinical outcome at days 10 to 14.

There are 5-day dosing studies again. These are the ones that supported the original application, a 3-day study I reviewed this morning and R-0581 here supporting the single-dose therapy. In general one can see that the difference in success rates was small in each of these studies and a pooled analysis of approximately 3200 patients comparing azithromycin with amoxicillin/clavulanate and again here in analysis of almost 4000 patients comparing all the patients in this program one can see that the difference in success at day 14 was less than 2 percent with very narrow confidence limits.

This is for us to examine the outcome of children treated with a single-dose of azithromycin for acute otitis media due to Hemophilus at the day 10 to 14 time point relative to other approved therapies.

Presented here is the 95 percent confidence interval on the point estimate of success for antibiotics that are approved for treatment of acute otitis media and clinical outcome data at day 14 for patients with

Hemophilus isolated at baseline.

For reference the outcome of patients given a single dose of azithromycin is up here and again we have the dashed lines that give the upper and lower limits of the 95 percent confidence interval. Again, these are point estimates of success.

The same cautions we noted previously about comparisons between the drugs are important. With those caveats, however, the outcome at day 14 for children with acute otitis media due to Hemophilus and treated with a single dose of azithromycin is comparable to other therapies.

In conclusion then we find that the data presented this morning demonstrate that azithromycin given as a single dose or over 3 days is an effective empiric treatment for acute otitis media.

Adverse event rates were similar or lower than the comparator and are generally limited to the gastrointestinal tract.

We believe that these shorter courses of therapy will optimize compliance while easing the burden on the care giver.

Thanks for your attention. I would be happy to answer any questions.

DR. RELLER: Thank you, Dr. Dunne.

Questions for Drs.Dunne or O'Rourke from the Committee.

Dr.Chesney?

DR. CHESNEY: Would you mind reviewing Slide No. 104 for us again, please?

DR. DUNNE: Main body presentation No. 104, please?

I will go over this again. This is data taken from studies in adults. It is pharmacokinetic data. It looked at different formulations of azithromycin. They were given as 2 grams as a single dose or 3 grams and there are different groups you can see in each study depending on the formulation that they received.

These are the PK parameters that were collected and this particular slide looks at area under the curve. The red triangles here are the means, and there is a standard error bar around each of the means.

The green triangles here, so this one, this one, this one here, here, here, these are individual values. They are individual AUCs for the subjects that vomited at greater than 2 hours, right? Yes, greater than 2 hours post-dose.

The yellow triangles are the AUC measurements for

the individual patients that vomited within the 2-hour window, and then we highlighted the ones that vomited even within 30 minutes and that is as you can see there in the purple dots.

DR. CHESNEY: Those weren't levels drawn from the patients though?

DR. DUNNE: I am sorry.

DR. CHESNEY: Were those levels drawn from the patients?

DR. DUNNE: Yes. These are the individual patient's data. So, we have a mean in red and in the individual patient in the yellow or the green to give you a sense of where they fit in and our conclusion from this particular slide here is that even if you vomit after getting the dose of azithromycin you still see to be absorbing it, and you might ask how could that be, you know, you gave them the drug and they are vomiting it up; how does that work?

The first thing to think about is that the amount of drug that is delivered either in this situation or actually in the pediatric trials is very small. It is only 2 teaspoons, 10 cc's. It is actually very hard to bring that back up. It actually lines the stomach wall.

Another thing that is important is that if it is

treatment-related vomiting that tends to recur when the drug has reached the duodenum the distal parts of the duodenum. By the time a drug is there, the pyloric sphincter will have closed if you start to vomit.

In other words by the time a drug is getting out to the place where it is causing you to vomit you are already absorbing it and even if you do vomit there is very little actual substance in there to come back up. So, it all kind of fits together when we look at the PK data and the clinical outcome data for us.

DR. CHESNEY: Just one more question along these same lines. Do we have any pharmacokinetic data from children using the single-dose therapy?

DR. DUNNE: No, we don't have any PK data in children per se at the 30-milligram-per-kilo single dose.

DR. CHESNEY: Were any children redosed if they vomited within half an hour?

DR. DUNNE: Yes, there were. There were eight children that were redosed if they vomited within the 30-minute window.

DR. RELLER: Dr. Glode?

DR. GLODE: I had three short quick questions, I think. One would be in the information we were given, the briefing document there is reference to modified intention

to treat analysis.

Could you just review what is modified in intention to treat?

DR. DUNNE: Yes. Actually let me put up the slide that shows kind of how we analyzed the patients? They are all kind of the same. So let us put up main slide No. 85, please?

Patients who were analyzed at day 28 had to receive a dose of drug. So, if you randomized and then left the clinic you would not be included.

You had to have a diagnosis of acute otitis media at baseline. I think just about everybody had that, but that was a rule and in this particular study you had to have shown up, actually in all of the studies you had to have shown up at the day 28 visit.

That means that the rule generally was that missing data was excluded from this particular analysis.

DR. GLODE: Thank you.

Then, and please excuse me. You presented so much data that I may have gotten this wrong, but it looked to me like the failure rate in the Costa Rican study was 6 percent for the day 28 overall failure rate and then in your subsequent studies that were done at multicenters in the United States they are pretty consistently in the range

of sort of 25 to 26 percent per single dose?

DR. DUNNE: Yes.

DR. GLODE: What do you think is the explanation for that?

DR. DUNNE: It is hard to know. That is a single center. So, within that 25 percent of the overall for the other studies there could have been centers that were higher or lower around that. It is a single center study.

DR. GLODE: My third question is that you said, "And as expected the failure rate in all these studies is much higher for children less than 2 than greater than 2." Why do we expect that?

DR. DUNNE: It has been seen in all of the studies that have used whatever antibiotic in treatment of those children.

DR. GLODE: But what are the possible explanations or what has been excluded? For example, is the rate of recovery of pathogens, bacterial pathogens different? If you do a tympanocentesis on less than 2 year olds versus older than 2 year olds, are we treating more non-bacterial disease in those children? I mean just sort of biologic plausibility I need an explanation.

DR. DUNNE: I think that you, I will just speculate here just for a second. A respiratory tract

infection, of course, can occur because of host defense problems in addition to a particular pathogen that has come and taken advantage of that host defense issue. I think the children under the age of 2 are likely to have more host defense issues. The angle of the eustachian tube is a little different. The antibodies they may have to the various bugs are at different levels than the older children. There are different developmental issues which may be playing a role in the outcome of children under 2 rather than over 2. So, it could be other epidemiologic variables which get folded in there as well, day care center attendance, for example, other things that could be important.

So, there is probably a collection of reasons.

DR. GLODE: And has anybody analyzed the tympanocentesis studies to see if the rate of recovery of a bacterial pathogen is different in the younger children than the older children? That would be of interest, and that information is available, I guess, just could be analyzed that way.

DR. DUNNE: Let me just look and see for a second if we have something along that line.

DR. RELLER: While Dr. Dunne is looking up this information, Dr. Marchant had a comment to make.

DR. MARCHANT: There is a study in the brochure that the Food and Drug Administration handed out by Carlin which shows that it is the exact data that you are asking for and it shows that the patients that, in patients whom you fail to eliminate the organism on average younger than those where the organism, sorry. Patients who eliminate the organism are older than patients who fail on average, the mean age.

So, young age is associated with failure to eliminate bacteria from the ear, and there is parallel clinical data in other trials that show the age effect on a clinical basis.

DR. DUNNE: I can just answer the one question. I think we will have to go back and look that up for you specifically. We had outcome data by bug. That is not the same question that you asked. So, we will have a look at that and see if we can bring it back after the break.

DR. RELLER: Dr. Wald had a question.

DR. WALD: Specifically though, Colin, I think that the question is is there a lesser frequency of recovery of bacterial pathogens in children less than 2 years of age, and I think the answer is no.

DR. MARCHANT: Right.

DR. WALD: I think that is the answer to your

question that frequency of recovery of bacterial pathogens in children under 2 is not less.

I really enjoyed your presentation. I think you did a very nice job, but there are two issues that really I find perplexing. In every study of the epidemiology of acute otitis media children under 2 are the largest age incidence group. Maybe two-thirds to 70 percent of all children with acute otitis media are under 2. So, I am a little bit surprised that in every one of your studies that this more-difficult-to-treat age group is in fact under represented. That is sort of question No. 1, and question No. 2 is that in the two tympanocentesis studies that were done the recovery of bacterial pathogens was only 50 percent, and I think that is a little bit less than we expect and my suspicion is that when children are selected for tympanocentesis one is very stringent in applying criteria because you really want to recover a bacterial pathogen.

So, that makes me really worry about the studies in which there was no tympanocentesis.

DR. DUNNE: I will start with the first question if I can make sure I have got that clear. Why is there only say 40 percent of the patients in these studies include children under the age of 2 whereas you might expect 50 or

60 percent in the clinical population? Yes, it is an enrollment into studies issue, and it may be that some parents with children under the age of 2 are less likely to enroll their children in a trial compared to what you might see in the community. I can say specifically within the studies, again, enrollment was allowed under the age of 2 and the investigators were free to enroll anyone that they wanted to but these are the data that we kind of got.

On recovery of organisms, I think 50 percent recovery in these types of studies is probably not far off from what is seen typically; certainly in the studies that we have done it is not far from what has been presented.

I wouldn't doubt that in other settings you might be able to get a higher rate of recovery. Say in a clinical practice setting you know the patients and there is more follow-up but the 50 percent mark is about what we have seen in other studies that we have done.

DR. RELLER: Dr. Gorman and then Dr. O'Fallon.

DR. GORMAN; As a pediatrician it is nice to see some recognition of host factors. Knowing we stand in front of the Anti-Infective Committee the microbiology discussion was very elucidating to me, but there are a few other host factors involved, and I was glad to see that those were mentioned at least briefly.

You had a lot of data about failures and successes over and under 2. Was any of that failure or success related to the adverse event and discontinuation of the medication, either yours or the comparator agent?

DR. DUNNE: So, to repeat the question --

DR. GORMAN: The data showed that there was a higher failure rate in children under 2. Was that related to the adverse events and the discontinuation of medicine secondary to adverse events?

DR. DUNNE: For the patients who received azithromycin there was a 99 percent compliance rate. So, we wouldn't have seen failures due to discontinuation of therapy in the azithromycin group. We didn't analyze the data specifically to look at compliance with the amoxicillin/clavulanate arms, for example, to see if that correlated with failure or not. Typically you need fairly large sample sizes to get a sense of compliance giving you efficacy correlations. So, I don't think I can answer that fairly for you, but it wasn't an issue for the azithromycin-treated patients if they altered their drug.

DR. RELLER: Dr. O'Fallon?

DR. O'FALLON: You set me up. My question right from the "get-go" has been about how compliance was defined since compliance is obviously a major issue for this

particular application. In those two double dummy type studies R-0581 and 1014 I read trying to figure out just exactly what it meant. They say, "The double dummy," but what we have here in one case is 3 days of active treatment and the other one 1 day of active treatment, and versus 10 days twice a day.

Now, how was that double dummy managed?

DR. DUNNE: You are right. You couldn't assess compliance during the course of the study because it was blinded. You could only do that after we had the data in house and we unblinded the data because the compliance measures that we used for these particular analyses looked at people taking their active study drug.

DR. O'FALLON: That is what I was afraid of.

DR. DUNNE: Yes.

DR. O'FALLON: Now, you are saying, let me just make it the worst case, you have got the one shot drug versus the twice a day for 10 days drug and now were the kids with the one shot getting a pill plus these two dummy pills for 10 days?

DR. DUNNE: Yes, the regimen would be that everybody got that first azithromycin dose either active or placebo right there in the clinic and they would then start that same time point their b.i.d. for 10-day dose.

So, after they left the clinic they were taking their b.i.d. doses.

DR. O'FALLON: Right, and half of them, the ones were getting, okay. So, now, when we talk about compliance, now what are you talking about if the kids on the one shot, the true active stopped taking their dose at 4 days, did they count as being compliant because they had their drug whereas the ones who were on augmentin had to have all 10 days or 8 days of it anyway, 9 days of it?

DR. DUNNE: Yes, that is an important point of the whole presentation. Let me see if I can clarify that for you. The idea of those presentations was to say, "How likely is it that someone will take their single dose versus how likely is it that someone will take 10 days of therapy?" That is kind of the question.

Now, there is a number of methods one can do to get at that. We chose the method of looking at compliance with your active study drug. So, basically the children who were assigned to augmentin retrospectively now we can look back and see who they were. We looked at the number of days that they took their therapy and if you were fully compliant you were fully compliant. Obviously if you were not you were less compliant.

Now, we could do other analyses of course. You

could look at the people who were given azithromycin active and took placebo augmentin and see if they took their placebo compliantly. That is another approach. I suspect that because it was randomized you will see a similar outcome.

DR. O'FALLON: You didn't show us that.

DR. DUNNE: Would you like to see that?

DR. O'FALLON: Yes, you didn't show us that.

DR. DUNNE: We will do that for you.

DR. O'FALLON: Because by definition the one drug is going to have 99 or 100 percent compliance.

DR. DUNNE: Sure. You know, it is an interesting question. How do you study compliance? And how does otherwise somebody study that? It is easy to just kind of walk beyond that in our data sets and say, "Well, of course."

Let us look at whether there really is a difference, and I think we see that there is a difference.

DR. O'FALLON: And the parents, that was the other thing. I had two technical questions about what you asked, I mean what you were showing. I couldn't absorb it quickly enough. The adverse events per patient year, what is that?

DR. DUNNE: Okay, let us go into that. We have a

few slides to help you with that.

I will flip through my book.

DR. O'FALLON: I didn't write down the number unfortunately.

DR. DUNNE: That is okay. We have it up here. Let us try looking at what exactly it is. First let us look at what I showed and then we will go back and see how did we get that.

Okay, so we will go to the main presentation and that is going to be Slide 99. Okay, good.

The backdrop to all of this is the top line here looks at patients that had an adverse event. So, if at any time after you randomize you had an adverse event you raise your hand, yes, but it doesn't get at the burden of side effects, how many did you have, how many days did you have them? So it is a fair analysis of the subjects with the adverse event. That is fair, but there may be more dimension to this when we are looking at the same total dose but delivered in different ways. So, we attempted to look at something that we actually don't normally do which is total burden of side effects in this particular program.

Okay, now, let us go to the safety slide No. 17 please?

So, this is a kind of a basic sense of what we

are doing. This is a patient, for example, who had a vomiting adverse event on day 1 and day 2, nausea on day 1, 2 and 3 and a headache on day 3 and 4.

In that top line of the analysis they get a one. Yes, I had a side effect. We miss all the other burden in here by doing that. So, what we tried to do was basically add up the X's. That is the approach. You look at the number of adverse events they had and the number of days that they had that.

Now, in order to compare one arm to another we had different numbers of patients and we had to normalize it to something. So, we just picked patient years' exposure, but how that works is you have a 30-day observation period when you are in the studies.

So, we just normalize that 30; that is the same for 1, 3 and 5, and then you just normalize that out to a year. That helps us deal with the big N. Okay? Does that help enough?

DR. O'FALLON: Yes, I see the concept, and I think it is a good analysis, I would say. There are different ways to do it, but that is good.

DR. DUNNE: Okay, thank you.

DR. O'FALLON: And finally, one more thing. On Page 54, I guess I wrote the page.

DR. DUNNE: This is of the briefing document?

DR. O'FALLON: No, your presentation, No. 107 and this happened on the other one as well. You keep just saying, "Percent successful clinical outcome," with a confidence interval on there, but I don't know which way the difference is defined.

DR. DUNNE: Okay, yes.

DR. O'FALLON: I cannot tell from this one. Other ones you showed but these don't, and I don't know what that confidence interval is.

DR. DUNNE: I want to make sure I have the right slide for you.

DR. O'FALLON: I have 107 and 108, either one of them.

DR. DUNNE: Let us put slide 107, say, for example? Yes, now, this is very important actually. In the previous tonados(?) there we have the difference in clinical outcome. So, it is the confidence interval on the difference.

DR. O'FALLON: But defined which way, which drug is first and which one is second?

DR. DUNNE: Great. I will go back to that. Why don't we go back to that. Let us just go back to Slide 106 then.

DR. O'FALLON: That one it defines it.

DR. DUNNE: Yes. Okay, so, this is confidence interval on the difference. The right side we favor azithromycin. The left side we favor comparator.

Now, we come to the next slide, 107, and we are switching things on you now.

DR. O'FALLON: That is what I was wondering because this doesn't look good for you if you kept it the same way.

DR. DUNNE: Yes, what this is is the confidence interval on the point estimate of success. So, it is not a difference anymore.

DR. O'FALLON: Oh.

DR. DUNNE: It is just the point estimate of success and there is a certain number of observations in that point estimate, and that gives you a 95 percent confidence interval.

So, we just presented this for data for a quick reference about how this, how our drug would look compared to what else is out there.

DR. O'FALLON: But what is the 80 to 95 percent business? What does that mean?

DR. DUNNE: Okay, yes. Those are the upper and lower limits of the confidence interval on that point

estimate. So, here is the point estimate here. It is about 88 percent.The lower limit is down here, 81 percent. The upper limit would be something like 95 percent. So, it is just for reference because otherwise there are lots of lines there. It is hard to find the azithromycin single dose regimen. So, we just labeled it out there for you.

DR. O'FALLON: Okay.

DR. DUNNE: Okay?

DR. O'FALLON: Yes, I will have to look at that. Thank you.

DR. RELLER: We have a series of questions now. Dr.Christie and then Ebert and Glode and Leggett, and then we have a break, and we can come back if there be questions for Dr.Dunne in the discussion later, I am sure he will be happy to answer those.

So, we will have the four queries on the table and then our break.

Dr. Ebert?

DR. EBERT: My question pertains to the end of treatment assessment. Could you just review the difference between a clinical cure and a clinical improvement as far as the criteria?

DR. DUNNE: Yes. Just to repeat your question, the question is what is the difference between clinical

cure and clinical improvement. The protocol gives a lot of leeway to the investigator to make decisions about improvement or cure.

Cure is complete resolution of signs and symptoms. So, they are all gone, but as I pointed out there could be a little sign of effusion left at any of those time points that would not preclude the investigator from calling it a cure.

Improvement is something shy of that. There is not quite resolution to feel comfortable that the child is cured. There may be a little bit of irritability left. There is some kind of sign or symptom which they are not happy is completely resolved, but it is better than baseline, and it is certainly not worse.

DR. RELLER: Dr. Christie?

DR. CHRISTIE-SAMUELS: Thank you. Do we know anything about whether or not the Hemophilus influenzae bacteria were typed and do we know anything about rate of HiB vaccination usage in Costa Rica as compared to here in the United States?

DR. DUNNE: Okay, so, two questions. Was the Hemophilus typed? Was it non-type O; was it type B? I assume that is the question, and the second was about vaccine, I am sorry, which vaccine?

DR.CHRISTIE-SAMUELS: Hemophilus influenza Type B vaccine. Is it used in Costa Rica?

DR. DUNNE: In 1995, I am actually not sure. We will have to go back and check that for you. I am not sure if that was -- that data was not collected as part of the program whether they had had Hemophilus influenzae vaccination or not but we can check with the investigator to see.

The other question was was the Hemophilus typed. No, we didn't do specific typing for Hemophilus as part of the program. Presumably the later cases, the ones in the more recent studies probably had a low incidence of Type B, but we didn't actually do typing on those Hemophilus.

DR. RELLER: Dr.Glode?

DR. GLODE: My question was just about that table 107. You have just explained now clinical cure versus clinical improvement, but what is clinical success?

DR. DUNNE: Clinical success is a combination of cure plus improved. Yes, that is a little regulatory thing.

DR. RELLER: And finally,Dr. Leggett?

DR. LEGGETT: I have a question regarding Hemophilus influenzae and this question of effusions and improved versus cure. Fifty percent of H. flu isolates more or less revert spontaneously to sterility and yet the

statement is made on Page 4 of your briefing document and was made here that they are, quote, difficult to cure.

What does that mean?

DR. DUNNE: I think the implication of that statement was not so much that in the short term the organisms could not be reduced in burden or there couldn't be some immediate cure rate, but it is difficult to completely eradicate that organism and the infection due to that organism.

So, in other words the overall success rate as you go farther out to day 28 later seemed to be a little lower for Hemophilus patients than it is for Strep. pneumo patients for example.

So, ultimately as Dr. O'Rourke kind of told us it may be more difficult to ultimately clear away that infection.

DR. LEGGETT: I don't remember seeing in Dr. O'Rourke's presentation, and maybe you can give us the data, was the relapse rate or that incidence of new infections higher for H. flu than it is for Pneumococcus? Is that the proposed -- and then how do we then wrap that around the fact that Pneumococcus is much more likely to cause acute otitis media than H. flu? I am having trouble with those concepts.

DR. DUNNE: I am trying to think of what I can help you with from the data that we collected.

DR. LEGGETT: That is sort of a problem, isn't it?

DR. DUNNE: Yes. I am not sure that we have data within the program to get specifically at the reasons for why it may be more difficult to treat Hemophilus, why there might be a lower overall success rate within the program. I will tell you we can go back and think about that and bring it back to you.

DR. LEGGETT: My question is what caused, what was your definition clinically of failure? Was it that the ear had to be red? Was it just that there was an effusion? That is what I am getting at.

DR. DUNNE: I think we have a breakdown by who failed and who cured and what their symptoms were. Maybe that would help a little bit.

DR. RELLER: We can go at ten-forty-five for the FDA presentation and questions from the general audience we will take care of in conjunction with the public presentation.

Thank you.

(Brief recess.)

DR. RELLER: The FDA presentation will be by Dr.

Moledina.

Dr.Moledina?

DR. MOLEDINA: Good morning. I am Dr. Nasim Moledina from Division of Anti-Infective Drug Products and as you must have figured out by now the discussion of topic today is single dose and 3-day treatment of azithromycin suspension in pediatric patients with acute otitis media.

With that as a background I would like to sort of summarize what is currently approved for acute otitis media as a 5-day regimen, not acute otitis media as a 5-day regimen in adults and in children for the indications for Zithromax and in adults for the 5-day dosing regimen it has been approved for acute bacterial inflammation of chronic bronchitis, pharyngitis/tonsillitis, community-acquired pneumonia and uncomplicated skin and skin structure.

In children azithromycin 5-day dosing regimen has been approved in acute otitis media, pharyngitis, tonsillitis and CAP and the indication reads that it is approved for acute otitis media caused by the three most common organisms, H. flu, M. catarrhalis and Strep. pneumoniae.

The dosing regimen is given as 30 milligram per kg total dose given as 10 milligrams per kg on day 1 and 5 milligrams per kg on days 2 through 5.

Basically I would like to give a background on how this drug was approved as a 5-day treatment and you have already heard from the sponsor that on day 30 for this 5-day approval. I would just like to point out the end of treatment data which was on day 11 for the three studies that were submitted in support of this, the original oral suspension.

The first study was study 134 and just to give you an idea, the success rate which now you know what success means, it means cure plus improvement and day 11 was the end of therapy evaluation point where azithromycin and the comparator both had a cure rate of 88 percent.

The 30-day data was already presented by the sponsor. So, I am not going to go through those. When you look at the second study which was a non-comparative clinical and bacterial study the success rate at the end of therapy was 84 percent for azithromycin.

This study, also, had data collected where there was baseline tympanocentesis done and this is for the end of therapy in this column and you look at the patients with Strep. pneumo isolated at baseline, 82 percent were cured compared to 80 percent in the H. flu group and 80 percent in the M. catarrhalis group.

There was a study, 128, which was, also, a